Title: Synthetic Heparin-Binding Factor Analogs

## IN THE CLAIMS

Please all prior versions and claims listing with the following claims listing: Claims listing:

1. (withdrawn) A henarin-binding growth factor (HBGF) analog of formula I:

$$R_1$$
  $R_2$   $Y$   $Z$   $X$   $X$   $X$ 

wherein:

each X is a peptide chain that (i) has a minimum of three amino acid residues, (ii) has a maximum of about fifty amino acid residues, and (iii) binds a heparin-binding growth factor receptor (HBGFR);

 $R_1$  is an amino acid residue, wherein X is covalently bonded through the N-terminus of  $R_1$  or through a side chain of  $R_1$ ;

 $R_2$  is a trifunctional alpha amino acid residue, wherein X is covalently bonded through a side chain of R:

Y is a linker comprising a chain from 0 to about 50 atoms covalently bonded to  $R_1$  and Z when n=0, or to  $R_2$  and Z when n=1;

Z is a non-signaling peptide chain that comprises a heparin binding domain, comprising an amino acid sequence that comprises (i) a minimum of one heparin binding motif, (ii) a maximum of about ten heparin binding motifs, and (iii) a maximum of about thirty amino acids; and.

n is 0 or 1, wherein when n=1 the peptide chains X are identical.

 (withdrawn) The heparin-binding growth factor analog of claim 1 wherein X and Z are synthetic peptide chains. AMENDMENT AND RESPONSE UNDER 37 CFR § 1.111

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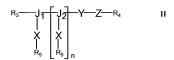
3. (withdrawn) The heparin-binding growth factor analog of claim 1 or 2 wherein Y further comprises a linker that (i) is hydrophobic, (ii) comprises a chain of a minimum of about 9 and a maximum of about 50 atoms, and (iii) is not found in the natural ligand of the heparin-binding growth factor receptor (HBGFR) which X binds.

- 4. (withdrawn) The heparin-binding growth factor analog of claim 1 or 2 wherein  $R_1$  is a trifunctional amino acid residue, wherein X is covalently bonded through a side chain of  $R_1$ .
- 5. (withdrawn) The heparin-binding growth factor analog of claim 1 or 2 wherein the heparin-binding growth factor analog has an avidity for heparin such that the synthetic heparin-binding growth factor analog binds heparin in 0.15 M NaCl, but is cluted by 1 M NaCl.
- 6. (withdrawn) The heparin-binding growth factor analog of claim 1 or 2, consisting essentially of a molecule of formula (I).
- (withdrawn) The synthetic heparin-binding growth factor analog of claim 1 or
   consisting of a molecule of formula (I).

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8. (previously presented) A heparin-binding growth factor (HBGF) analog of formula II:



wherein:

 $R_3$  and  $R_5$  are each independently  $NH_2$ , an acyl group with a linear or branched  $C_1$  to  $C_{17}$  alkyl, aryl, heteroaryl, alkene, alkenyl or aralkyl chain including an N-terminus  $NH_2$ ,  $NH_3^+$ , NH group or a corresponding acylated derivative, or is an amino acid, a dipeptide or a tripeptide with an N-terminus  $NH_2$ ,  $NH_3^+$ , NH group or a corresponding acylated derivative:

 $R_4$  is -OH, NH<sub>2</sub>, NH-R<sub>6</sub>, or is an amino acid, a dipeptide or a tripeptide with a C-terminus -OH, NH<sub>2</sub>, or NH-R<sub>6</sub>;

R<sub>6</sub> is an aliphatic C<sub>1</sub> to C<sub>17</sub> chain;

each X comprises a peptide chain that is selected from SEQ ID NO: 6-21;

 $J_1$  and  $J_2$  are each independently a trifunctional alpha amino acid residue, wherein each X is covalently bonded through a side chain of  $J_1$  or  $J_2$ :

Y is a linker comprising three amino hexanoic acid residues;

Z is a non-signaling peptide that comprises a heparin binding domain, comprising SEQ ID NO: 2;

n is 0 or 1, wherein when n=1 the synthetic peptide chains X are identical.

9. (original) The heparin-binding growth factor analog of claim 8 wherein X and Z are synthetic peptide chains.

10-11. (canceled)

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12. (previously presented) The heparin-binding growth factor analog of claim 8 wherein the heparin-binding growth factor analog has an avidity for heparin such that the heparin-binding growth factor analog binds heparin in 0.15 M NaCl, but is cluted by 1 M NaCl.

## 13-14. (canceled)

- 15. (currently amended) The heparin-binding growth factor analog of claim 8 wherein  $J_1$  is, and [[,]] if n = 1,  $J_1$  and  $J_2$  is a diamine amino acid residue.
- 16. (original) The heparin-binding growth factor analog of claim 15 wherein the diamine amino acid residue is a 2,3 diamino propionyl amino acid residue.
- 17. (original) The heparin-binding growth factor analog of claim 15 wherein the diamine amino acid residue is lysine.
- 18. (original) The heparin-binding growth factor analog of claim 15 wherein the diamine amino acid residue is ornithine.
- 19. (currently amended) The heparin-binding growth factor analog of claim 8 wherein the covalent bond between X and J<sub>1</sub> or, if n=1, J<sub>1</sub> and J<sub>2</sub>, comprises a peptide, disulfide, thioether, Schiff base, reduced Schiff base, imide, secondary amine, carbonyl, urea, hydrazone or oxime bond.
- $20. \ \, (currently\ amended) \qquad The\ heparin-binding\ growth factor\ analog\ of\ claim\ 8 \\ wherein\ the\ side\ chain\ of\ J_1\ and,\ if\ n=1,\ \underline{J_1\ and}\ J_2,\ comprises\ a\ reactive\ carboxyl\ group.$

21. (withdrawn) The heparin-binding growth factor analog of claim 8, 9 or 10 of formula III:

wherein m is from 1 to about 10.

22. (withdrawn) The heparin-binding growth factor analog of claim 21 of formula IV:

wherein p is from 1 to about 10 and q is from 1 to about 20.

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23. (withdrawn) The heparin-binding growth factor analog of claim 22 wherein p is 5, q is three, Z is SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 or SEQ ID NO:5, and X is SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20 or SEQ ID NO:21.

24. (withdrawn) The heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein the peptide chain X has a minimum of approximately five amino acid residues.

25. (withdrawn) The heparin-binding growth factor analog of claim 24 wherein the peptide chain X has a minimum of approximately nine amino acid residues.

26. (withdrawn) The heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein the peptide chain X has a maximum of approximately thirty three amino acid residues.

27-31. (canceled)

32. (previously presented) The heparin-binding growth factor analog of claim 8 wherein the heparin-binding growth factor analog binds an FGF receptor.

33-36. (canceled)

37. (previously presented) The heparin-binding growth factor analog of claim 8 wherein the peptide chains X are cross-linked or cyclized.

38. (original) The heparin-binding growth factor analog of claim 37 wherein the peptide chains X are cross-linked or cyclized by at least one disulfide, peptide, or thioether bond.

39-45. (canceled)

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46. (withdrawn) A pharmaceutical composition comprising the heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 or a pharmaceutically acceptable salt thereof and a pharmaceutical carrier.

47. (withdrawn) A method for treating a mammal that is exposed to a harmful dose of radiation or a chemotherapeutic agent, the method comprising administering to the mammal an effective dose of a heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22.

48. (withdrawn) A method for treating a mammal that is exposed to a harmful dose of radiation or a chemotherapeutic agent, the method comprising administering to the mammal an effective dose of a heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22 wherein X binds an FGF receptor.

- 49. (withdrawn) The method of claim 47or 48 wherein the dose of radiation or chemotherapeutic agent is sufficient to cause mucositis, G.I. syndrome, or radionecrosis.
  - 50. (withdrawn) The method of claim 48 wherein the FGF receptor is an FGF-7 receptor.
- 51. (withdrawn) A method for stimulating growth factor receptor signaling in a cell, the method comprising contacting the cell with an effective amount of a heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22.
- 52. (withdrawn) The method of claim 51 wherein the signaling stimulates proliferation of the cell
  - 53. (withdrawn) The method of claim 52 wherein the cell is part of a mammal.
- 54. (withdrawn) A method for delivering an active heparin-binding growth factor analog to a mammal, the method comprising:

providing a medical device coated on the surface thereof via non-covalent bonds with a synthetic heparin-binding growth factor analog of claim 1, 2, 3, 8, 9, 10, 21 or 22; and

placing the medical device onto a surface of, or implanting the medical device into, the

55. (withdrawn) The method of claim 54 wherein the medical device is a suture, graft material, wound covering, nerve guide, bone wax, aneurysm coil, embolization particle, Title: Synthetic Heparin-Binding Factor Analogs

microbead, stint, dental implant, or bone prosthesis, a tissue scaffold or a controlled release drug delivery device.

- 56. (withdrawn) The method of claim 54 wherein the non-covalent bonds are associations between the heparin-binding domain of the synthetic heparin-binding growth factor analog and a heparin-containing compound bound to the surface of the medical device.
- 57. (withdrawn) The method of claim 56 wherein the heparin-containing compound is benzyl-bis(dimethylsilylmethyl)oxycarbamoyl-heparin.
- 58. (withdrawn) The method of claim 54 wherein the surface of the medical device is stainless steel, titanium, platinum, tungsten, ceramics, polyurethane, polyeterafluoroethylene, extended polytetrafluoroethylene, polycarbonate, polyester, polypropylene, polyethylene, polystyrene, polyvinyl chloride, polyamide, polyacrylate, polyurethane, polyvinyl alcohol, polycaprolactone, polyactide, polyglycolide, polysiloxanes, natural rubbers, artificial rubbers, block polymers, or copolymers of block polymers.
- 59. (withdrawn) The method of claim 58 wherein the polysiloxane is 2,4,6,8-tetramethylcyclotetrasiloxane.